

ROUTING SLIP
GENERATED BY: HF-40
DATE: AUG 02,2004

FDA CONTROL NUMBER: 04 4192

TRACER #: **OS #:**

DATE OF CORRESPONDENCE: 07/22/04

DATE INTO FDA: 07/27/04

TO: LESTER M CRAWFORD, ACTING COMMISSIONER OF FOOD AND DRUGS

FROM: GEORGE A BRAY, MD, LOUISIANA STATE UNIVERSITY - PENNINGTON BIOMEDICAL
RESEARCH CENTER

SYNOPSIS: SUBMITS COMMENTS ON DOCKET NO. 2003N-0338 REGARDING OBESITY; REF:
TRAC # 04-4 142.

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Pennington Biomedical Research Center
LOUISIANA STATE UNIVERSITY

Letter to Docket 2003N-0338

July 22, 2004

Lester Crawford, D.V.M., Ph.D.
Chair, Obesity Working Group
Deputy Commissioner FDA
5600 Rockville Pike
Rockville, MD 20857

Dear Dr. Crawford:

Re: CALORIES COUNT: Report of the Working Group on Obesity

I am George A. Bray, M.D., University Professor at the Pennington Biomedical Research Center of the Louisiana State University System in Baton Rouge, LA. I have worked in obesity for 40 years and have been continuously funded by the NIH during all that time. I chaired the first Fogarty Center/NIH Conference on Obesity in 1973, organized the International Journal of Obesity in 1975, founded the North American Association for the Study of Obesity (NAASO) in 1980, and founded and acted as first editor for Obesity Research, the official Journal of NAASO. I am submitting the following comments to the document CALORIES COUNT in the spirit of constructive suggestions based on my experience with the field. I am also enclosing a copy of a recent monograph that may be of use.

The Obesity Working Group of the FDA has done a commendable job in putting together a series of recommendations "centered on the scientific fact that weight control is primarily a function of balance of the calories eaten and calories expended on physical and metabolic activity" (Executive summary paragraph 5). There is no doubt that human beings are constrained by the First Law of Thermodynamics which describes the net effect of changes in energy input and output on energy (fat) storage. However, I would prefer to see "HEALTHY WEIGHT" as the title and focus for the following reasons.

I will divide my comments into two parts, general and specific.

General Comments:

1. I absolutely agree that obesity results from positive energy balance, and that if we knew enough we could predict the magnitude of the change over time. However it is what the energy balance concept DOES NOT TELL US that is most important in dealing with the current epidemic of obesity. The First Law does not tell us anything about the regulation of food intake or the way in which genes are

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involved in this process. It does not help us to understand why men and women have fat in different places on their bodies nor to understand how fat distribution changes with age. The First Law also doesn't help us to understand why some drugs can produce weight gain while others produce weight loss, or why the weight loss stops after a period of treatment with diet or medication. It is in the understanding of these mechanisms that our ability to tackle the epidemic of obesity may lie.

Another limitation in the theme of CALORIES COUNT is the implication that if you are fat, then it is your fault. It implies that all you need to do to be thin is to control calorie balance. It seems to me grossly unfair to "blame the children" for their obesity. If obesity were easy to control by moderating calorie intake, the U.S. military wouldn't discharge over 1,000 men and women each year for failing to meet "weight standards" and these men and women wouldn't lose their employment. If job loss isn't a sufficiently strong incentive to maintain calorie balance, then I suggest we need to look elsewhere.

Finally, we never achieve energy balance. In studies we have conducted in our metabolic chamber, we have measured energy balance while trying to keep the difference between calorie intake and calorie expenditure as close to zero as possible. On no day were subjects closer than 25 kcal/d and the swings were both above and below the balance point. We are not in energy balance today, nor were we in balance yesterday and we will not be tomorrow.

From the perspective of energy balance the solution to obesity is simple. Eat less and exercise more. This was the advice that Hippocrates, the Grecian Father of Medicine gave to his patients more than 2000 years ago. The truth of this advice was shown by Kinsell et al for overweight individuals housed in a metabolic ward and provided with all of their food. Over several months these patients ate diets with 1200 kcal/d. After the initial rapid weight loss due to rebalancing body fluids, subsequent weight loss was linear, and was not affected by wide variations in carbohydrate, fat or protein content of the diet. More recent studies using foods that were tagged with a non-radioactive isotopic carbon-13 showed that the better the adherence to a diet, the greater the weight loss. That is, it was adhering to the diet, not the diet itself, that made the difference.

2. Applying the First Law of Thermodynamics to the problem of obesity is similar to applying the laws of motion to automobile accidents. We know that when cars collide they dissipate the kinetic energy in the crash. If people drove slowly, never under the influence of alcohol and always obeyed the traffic signals there would be fewer accidents. Our efforts at reducing auto accidents are directed at the drivers and automobiles, not at the laws of physics. We use driver education, regulation and product design to reduce automobile injury and death. Similarly the First Law of Thermodynamics describes the consequences of eating more food energy than is burned in exercise and metabolism over an extended period of time. Preventing this imbalance requires manipulating the

environment in the same ways that modifying cars and road structures is done to reduce automobile accidents and injuries. The strategies for preventing obesity will no doubt include education, regulation and product design. A 2003 WHO document has outlined a number of strategies that might be useful in this context.

Specific Comments:

Introduction

1. The comments in the introduction are clearly stated and ones I completely agree with.

FDA Obesity Working Group

1. The description is very clear

Foundations of this report

A. Scientific Principles

1. I completely agree that obesity results from energy imbalance, but the implications of a strategy based on CALORIES COUNT troubles me.
2. The idea that “calories eaten should equal the calories expended on a daily basis” is nonsense, and deludes one into thinking this is possible when it is not. The net intake of energy from 50 cc of calorie-containing soda (1.5 oz = 5 g of HFCS from a 10% solution = 20 kcal) each day above energy needs would produce a 7,000 kcal surplus per year (about 2 pounds). We do not have instruments of sufficient sensitivity to detect this small error. The best we have is the bathroom scale. This is why I think you would do better to emphasize a “HEALTHY WEIGHT” where you have an instrument that could provide useful feedback over an interval of a week to a month. Nowhere in this report do I find the bathroom scale mentioned.
3. In terms of calories, I do not find the concept of pre-packaged portion control utilized. This is the one strategy using calories that has to this date proven useful in treatment.

B. FDA's Public Health Mission and Legal Authorities

1. Thank you for the description. I learned something new.
2. The idea of “regularizing” per serving nutrient value has real interest.

C. Stakeholder Participation. Thank you for letting me contribute, albeit, I probably do not constitute a “stakeholder”, just an interested research scientist.

D. The OWG's work

1. I wish to respectfully disagree with the interpretation of the knowledge base used here. I have made the argument under general comments above, but will do so again here. The FDA OWG proposes to build messages around the “theme of CALORIES COUNT” based on the scientific fact that net calorie gain or loss over time is the root cause of obesity.” Although this is true, it misuses the truth of a “state equation” which cannot describe the processes by which the changes occur. As I said above, it is what the energy balance concept does

NOT tell us that will be important in combating obesity. It doesn't tell us that cessation of smoking is associated with weight gain, suggesting that the nicotine in tobacco causes weight loss. Similarly it doesn't tell us why some drugs cause weight gain, others cause weight loss and still others have no effect on body weight.

In addition, the energy balance concept puts the "onus" for obesity on the obese individual. If it were that simple, we would have solved the problem during the early years of my 40-year career.

2. Sound nutritional advice, built around the concepts of variety and moderation and on healthy weight is worth providing through educational messages to everyone.

3. I was intrigued, but not at all surprised, that the messages you proposed didn't resonate particularly well. If these types of messages were of value, we would have solved the problem when I was Nutrition Coordinator in the Office of the Surgeon General 25 years ago. Because weight is gained slowly (10-20 kcal/d net surplus equals 1-2 pounds per year), calorie-based messages are simply not going to go any further now than they did 25 years ago. In fact, the development of the epidemic in the face of these messages suggests that the regulatory and product design aspects of the preventive solution will have to be more important than the educational one. This is also true for automobile accidents, which bring laws of physics to bear on human frailty. Traffic signals, speed limits, seat belts, child restraints and air bags have had more value in reducing accidents than "education".

A. Need for Education Programs

1. Another major concern with the education program is that it makes the victim responsible. In my view, obesity is a chronic, relapsing, neurochemical disease. I introduce the term "neurochemical" because it helps to take the "moral" aspects of self-blame and external blame off of the obese individual. The data on weight change with drugs, imprinting and neonatal experiences reinforce the use of the neurochemical concept. I would prefer to see you focus on this type of message rather than the "you are to blame" messages.

2. Your message of CALORIES COUNT will only exacerbate the problem you identify on page 12. If calories count, and calories come from food, then not eating food is a perfectly rational response. I would propose that you rethink this educational strategy if you don't want the consequence of "starvation" and "meal-skipping" particularly by the vulnerable adolescents who are concerned about their weight.

B. OWG Education Recommendations

1. I would like to see more emphasis on variety and moderation, "portion control foods," and healthy weight. This way you avoid the "meal-skipping" idea and reduce some of the personal responsibility for being obese.

2. As long as the energy dense foods (those with sugar, fat and low water content) remain cheap, and people have limited income, you will have a continuing problem with food choices.

3. The ideas on teaching 11-13 year old children how to make smart food choices and physical activity choices flies in the face of the longitudinal data showing that adolescent girls have a steadily declining level of energy expenditure.

4. Having worked on the first edition of the Dietary Guidelines, I think they can serve as a useful guide for the population. However, they now have more interest for the food lobbies than for the American population who have become obese in the face of these Guidelines.

Food Labels p. 15

1. Having labels that provide nutrition for the package size could be useful.

2. I have just returned from the UK where nutrition labels are per 100 g, with servings listed in large font on the front of the package. This was an easier system to use than ours.

3. Even though I am a physician with some knowledge of nutrition, I have never understood the %DV data. I would suggest that you remove it.

FDA Focus Groups on Food Labels

1. I am not surprised that consumers don't often consider nutrition when making food purchases. I don't either. In fact, I often shop on price per unit rather than nutrition.

1. The comment about "taste, convenience and price" has a lot of merit. I suspect that until the price advantages for the energy dense and tasty foods begin to lessen, our efforts at "nutritional" messages will have limited appeal.

OWG Food Label Recommendations

Calories and Serving Sizes

1. I like the idea of modifying the label for those who will read it, few as they may be.

2. I support the idea of re-examining regulations on serving sizes. One of the major changes in the food supply over the past 20 years has been the increase in portion size with corresponding increase in energy. Reducing portion size would be a good step forward. More small packages is one possibility, although these will be more expensive.

3. An additional step would be to design strategies to reduce the energy density of prepared and packaged foods.

4. As I said above, I would eliminate the %DV and the comparative intake levels.

Carbohydrate Labeling

1. One problem with labeling for carbohydrate is the analytical data. It is usually determined by "difference," meaning the errors of the other methods are included in carbohydrate.

Other Labeling Issues

1. I thought all of the comments from the FTC were very helpful.

2. Providing more information on restaurant foods would be helpful. If you saw *Supersize Me*, the movie about eating at McDonald's for a month, it made clear how hard it was for the writer to get the nutrient information that was supposed to be "displayed" in each restaurant.

C. Therapeutics

1. Through regulatory action, the FDA has removed two medications where the risk was small – PPA and ephedra. The estimated confidence interval for stroke for women taking PPA was 1/125,000 to 1/1 million. There are few drugs that have this low a risk. If I were a manufacturer, I would be concerned about the future of medications, because few if any can meet these standards.

2. On p 29 you refer to obesity as a "chronic condition". The recent Medicare and DHHS pronouncement might get you to agree with me that obesity is a "chronic relapsing, neurochemical disease."

3. The statement "maintenance of weight loss, even while on continued drug therapy is the rare exception rather than the rule." I would flatly disagree with you. The comparative trials lasting up to 4 years (XENDOS) show that the drug maintains its difference from placebo, although both groups over time are reflecting the rise in body weight seen in the obesity epidemic.

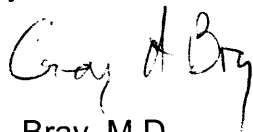
4. Here for the first time that I remember, you introduce "Healthy Weight". As I indicated earlier, I would be inclined to make this a focus of your programs. It provides a better message with broader implications and it does not put so much of the burden on the individual.

5. I have provided a detailed letter to the Agency about my thoughts on the FDA "Guidance for the Clinical Evaluation of Weight-Control Drugs". I have attached another copy.

6. In light of the current BMI recommendations that overweight is defined as a BMI of 25-29.9 kg/m², I would suggest that you include subjects in weight loss drug trials who have a BMI of 25 to 29.9 kg/m² with co-morbidities rather than the current 27-30 kg/m².

I am delighted to see that there is a follow-up conference scheduled for this fall. I will be most interested in its outcome.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "George A. Bray".

George A. Bray, M.D.
Boyd Professor

Encl: *Contemporary Diagnosis and Management of Obesity and the Metabolic Syndrome*; letter to FDA on guidance for obesity drugs



Re: Docket Number 2003D-0570:
Comments on Clinical Evaluation of Weight Control Drugs Guidance issued 9-24-96

Thank you for the opportunity to provide my ideas about the procedures for the Clinical Evaluation of Weight Control Drugs as outlined in your Guidance document of 9-24-96. Prior to the issuance of this Guidance, Dr. Leo Lutwak had convened an expert panel to give input to the FDA about this problem. One signatory to this letter (GAB) was one of those initial participants. More than a decade has passed since this conference, and we are pleased to provide you with our current ideas.

General Comment: We view the procedures for evaluating a drug in the treatment of obesity as an opportunity to demonstrate the efficacy of the drug and its high level of safety; considering the population in which it will be used, we also view this process as a basis for developing information about the use of a drug by physicians in the practice of medicine and the care of their patients.

Paragraph by Paragraph Comments:

1. Introduction: Well done.
2. General Rationale:
 - a. In the middle of this paragraph it says: "Since it is possible that a new "set point" will be developed at a reduced body mass, drug administration might be required for only a limited time"; for the purpose of drafting a new Guidance, this statement should be removed. We know of no evidence that obesity can be cured. Years ago, the rationale for the jejuno-colic by-pass was that when patients lost weight the operation would be reversed they would be able to maintain the lower weight. As Payne et al [1] found, to their chagrin, all of the patients regained weight after reversal. Since, in our view, obesity is a "chronic relapsing neurochemical disease" [2], it is only a matter of time after any treatment is discontinued before weight will return to "baseline". However, this doesn't mean that treatment needs to be "continuous". At least two studies using discontinuous therapy with anti-obesity drugs [3]; [4] demonstrate that anti-obesity drugs produce as much weight loss at 9 or 12 months as continuous therapy. Indeed, trials with intermittent therapy might be worth evaluating.
 - b. Weight loss has two components. One is medical and one is cosmetic. When health is at risk, the potential risks of a drug can be greater than when the goal is cosmetic. Since the majority of patients seek weight control for "cosmetic" reasons, safety concerns become more important than if people were only using them were for high risk of diabetes, gall bladder, cardiovascular or other diseases. Since the motivations for taking these medications will be the desire to "look good," and the desire to improve the quality of life is an important

medical end-point, recognition that anti-obesity drugs will have BOTH cosmetic and medical uses is important in designing trials and in developing information for the physician and consumer.

c. Length of clinical trials. Although anti-obesity drugs may have long-term use, for most consumers the continuous use is likely to be only a few weeks to a few months. This is true for two reasons. First, clinical trials for weight loss demonstrate that weight loss ceases after 4 to 8 months of treatment – a plateau develops. This occurs with behavioral, dietary, medical and surgical interventions. It is the nature of a homeostatic, compensatory system. However, when weight loss does reach a plateau that plateau is often less than 10% of initial body weight and many patients discontinue the medication because they conclude that the medication “isn’t working”. Moreover, discontinuation is more likely if the medication is expensive. We know from experience with over-the-counter herbal ephedra preparations that consumers will pay up to \$30/month for fairly long term use. However, we also know from the experience with sibutramine and orlistat that they will not pay \$100/month for an equivalent amount of weight loss. Thus the interaction of cost and the compensatory plateau make it unlikely that many consumers will use anti-obesity drugs for an extended time – at least not with any current drug. However, they will typically use them for short periods when weight loss is needed for cosmetic reasons such as a wedding, a divorce, a reunion or to achieve a personal weight goal.

3. Early Clinical Trials. The statement is very clear and useful.

4. Dose-ranging Finding. The criteria for designing the initial dose-ranging studies are clearly stated. Because only 75% of the maximal weight loss is achieved by 3 months, trials of 6 months might be more appropriate. We would also prefer the trial to begin without a “run-in” period, unless the run-in is to establish tolerability to the medication procedure without other active (lifestyle or diet) therapy.

5. We will take this section paragraph by paragraph.

5.1 Population: The current Guidance was written before the NHLBI and WHO provided uniform recommendations for classification of obesity. We would encourage the FDA to include in their trials individuals with a BMI > 25 kg/m² since all of our epidemiological data, particularly that for diabetes, shows that the risks of disease begin at that level. The selection of 27 kg/m² with co-morbidities harks back to the days when the NCHS was using the 27.3 and 27.8 kg/m² BMI unit cut-points to define overweight. Now that these cut-points are no longer used, the FDA might want to seriously reconsider its selection of 27 kg/m² and move to 25 kg/m². Measuring body fat can be useful, but the BMI and waist circumference have proven to be very useful criteria for assessing risk [5]; [6]; [7]. Measurement of waist/hip ratio and sagittal diameter have nothing over the simple measurement of waist circumference, and I would recommend that the waist circumference be used along with the BMI.

5.2 Procedures:

Subject Selection: We strongly object to the use of the run-in for clinical trials of anti-obesity drugs. It is confusing to the physician, to the patient, and not instructive for the effect of the drug. When a patient receives medication from a physician for the treatment of obesity, what both the doctor and patient want to know is how much weight loss their patient is likely to achieve, and what side effects might occur. The idea of “placebo-subtracted” weight loss is unhelpful to either physician or patient. Similarly, few physicians have the office set-up to conduct an active lifestyle change program or to give diet counseling. An effective anti-obesity medication will usually be used with minimal behavioral or lifestyle therapy. Thus, for both patient and physician, knowing how much weight loss is achieved from initiation of the drug is the question of interest, NOT how much weight loss might occur after an active lifestyle or dietary intervention. Thus, we think the run-in should be eliminated or shortened to a non-therapeutic period of 1 week.

We like the discussion of the weight maintenance strategies at the end of paragraph 5.2. These have proven to be very useful and important.

End-point evaluation. Since men and women are included and they have different percentages of body fat and often different initial body weights, we would prefer to have the primary end-point the Percent Change in Body Weight. Since height doesn't change, the change in BMI provides no more information than the change in body weight, and is a more cumbersome unit for weight loss. We would NOT just use change in BMI. Change in body fat in kg and % separated by genders would also be useful, as would changes in visceral adipose tissue in a subsample.

Weight loss demonstrations. We would prefer a criterion of >5% from baseline and significantly greater than placebo. At present, no drug consistently meets the criterion of 5% below placebo. To require a drug to be >5% below placebo encourages trials with a “weak” placebo effect to make it easier to see the 5% criterion. This in turn penalizes long-term trials, since patients on placebo losing only small amounts of weight are likely to drop out. Although we would like drugs to produce >10% below baseline as monotherapy, almost none have done so, and if this were the criterion, we might have no drugs at all. Moreover, for many people a weight loss of 5-10% is sufficient for the “cosmetic” effects that are often wanted. It will also produce significant health benefits [8]; [9].

The use of improvements in “risk” factors is good. We would drop sagittal diameter and use waist circumference. Studies in diabetic populations and hypertensive populations are valuable.

Since in many patients with recent onset diabetes, weight loss can lead to remission, it might be claimed that drugs producing weight loss are “anti-diabetic” drugs. We would not favor this position. If the drug doesn't have an independent

effect of glucose metabolism or the action of insulin, we would not favor approving it for diabetes. Weight loss in diabetics and pre-diabetics, on the other hand, is clearly beneficial, because it will lower the cost of treatment for diabetes and may lead to remission. Thus, weight loss drugs might be labeled as weight loss adjuncts for the treatment of diabetes.

Improvement in the quality of life is one of the major reasons that most people seek help with their weight. Having some measure of how much improvement there is would be valuable.

Except in the very obese, the issue of excess fluid does not exist. When we measured intracellular and extracellular water in a group of obese patients, the only ones with abnormal distributions were those who were “very” obese, i.e., more than 400 pounds. However, we think documentation of the extent of change in lean body mass and calcium loss (DXA bone changes) could be considered in a subset of patients.

5.3 Duration of Trials. We would propose that a 12-month double-blind, randomized, placebo-controlled trial should demonstrate 5% or greater reduction from baseline weight for the drug-treated group at 12 months that is also significantly lower than placebo. Viewing the 4-year XENDOS trial [10] the drug-treated group and placebo-treated group both began to regain weight following the plateau at 12 months, but the drug-treated group remained more than 2% below the placebo-treated group even after 4 years. Unless there is evidence of escape from the therapeutic effect of the drug as occurred with fluoxetine [11], we think that a 12-month trial is sufficient to show efficacy and safety.

The issue of follow-up and handling of drop-outs is an important one. Our experience with follow-up after discontinuation from a clinical trial is dismal. If patients quit they usually don’t want to be followed up by phone or otherwise. With our current IRB constraints the problem is even more difficult. For the package insert, we would propose that only the completers analysis be used. What the physician and patient both want to know is how much weight loss they might achieve if the drug is used for 12 months. Including patients who drop out lowers the apparent effect of the drug, and fails to give either patient or physician a clear idea of what to expect. We would thus propose using the completers analysis for informing physicians and patients.

Obesity, a chronic medical disease like hypertension or diabetes, has multiple and redundant control mechanisms. It is likely that, as with diabetes and hypertension, multiple medications working by different mechanisms will need to be employed for effective management. Since combinations of drugs have been approved for hypertension and diabetes, this raises the issue of combination therapy in the treatment of obesity, and the criteria for approving such combinations of drugs to treat obesity. The advantages of combination therapy are that lower doses of active medication might be used with fewer side effects,

or that the magnitude of weight loss might be significantly greater. To document these changes, clinical trials comparing active agents would be required after the approval of the parent compound. Strategies for reducing dosages and for increasing the magnitude of the response may require placebo-controlled trials lasting 6 to 12 months. Longer periods might not be needed, since each group would already have been approved with longer trials.

Thank you for the opportunity to respond to your Request for Comments on the Draft Guidance on the Clinical Evaluation of Weight-Control Drugs.

Sincerely yours,

George A. Bray, M.D.
Boyd Professor

Donna H. Ryan, M.D.
Associate Executive Director

Frank L. Greenway, M.D.
Professor, Chief Outpatient Clinic

Steven R. Smith, M.D.
Associate Professor, Chief In-Patient

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